Derivation of an Extrapolated Short-term Inhalation Screening Level for 4-Methylcyclohexanemethanol (MCHM – CAS# 34885-03-5)

U.S. Environmental Protection Agency (EPA)
Office of Research and Development (ORD)
National Center for Environmental Assessment (NCEA)
Superfund Health Risk Technical Support Center (STSC)

Background:

Currently, there are no available repeated-dose inhalation toxicity studies on 4-methylcyclohexanemethanol (MCHM) in humans or animals. There is a single short-term repeated-dose oral study conducted in rats. In this study, male and female CD(SD)BR rats (5/sex/dose group) were administered MCHM (purity >96%) via gavage at doses of 0, 25, 100, and 400 mg/kg-day, 5 days per week, for 28 days (Eastman Kodak Company, 1990). The lowest-observed-adverse-effect level (LOAEL) for this study is 400 mg/kg-day based on erythropoietic, kidney (increased tubular degeneration), and liver (increased weight and inflammation) effects. The associated no-observed-adverse-effect level (NOAEL) is 100 mg/kg-day. Detailed descriptions of all available toxicity studies for pure MCHM and crude MCHM can be found on the National Library of Medicine's Hazardous Substances Data Bank (HSDB, 2014).

There are no available toxicity values for MCHM from the U.S. EPA's Office of Solid Waste and Emergency Response (OSWER) recognized Tier 1–3 sources or the International Toxicity Estimates for Risk (ITER) database. Recently, the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry (CDC/ATSDR) established a short-term health advisory for MCHM in drinking water in and around Charleston, West Virginia after approximately 7500 gallons of the chemical was spilled into the Elk River (CDC/ATSDR, 2014). CDC/ATSDR's short-term drinking water advisory for MCHM of 1 part per million (ppm) is based on the NOAEL of 100 mg/kg-day from the aforementioned 28-day gavage study in rats. The drinking water (DW) advisory was derived to be protective of children as follows:

$$\text{DW Advisory} = (\text{NOAEL} \times \text{BW}) \div (\text{UF}_C \times \text{Intake})$$

$$\text{DW Advisory} = (100\ \text{mg/kg-day} \times 10\ \text{kg}) \div (1000 \times 1\ \text{L/day})$$

$$\text{DW Advisory} = 1\ \text{mg/L (or 1 ppm)}$$

Where:

- NOAEL = No-observed-adverse-effect level from 28-day gavage study in rats
- BW = Body weight of a child (10 kg)
- UF_C = Composite uncertainty factor ($UF_A \times UF_H \times UF_D$) applied to account for (1) uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability; $UF_A = 10$), (2) human-to-human variability in susceptibility and consideration of possible effects on vulnerable populations, including pregnant women and children ($UF_H = 10$), and (3) the limited availability of data and database deficiencies – e.g., lack of reproductive and developmental toxicity studies ($UF_D = 10$).
- Intake = Estimated drinking water intake of a 10 kg child (1 L/day).

Derivation of an Extrapolated Short-term Inhalation Screening Level:

Assessing the potential public health impacts of inhalation exposures to MCHM is difficult due to the lack of any available inhalation toxicity data. However, using CDC/ATSDR's short-term DW advisory for MCHM of 1 mg/L (or 1 ppm), it is feasible to conduct an oral route-to-inhalation route extrapolation in an attempt to estimate a short-term inhalation screening level. The methodologies and derivations presented herein were reviewed by scientists within the U.S. EPA and independently peer-reviewed by scientists at the CDC/ATSDR, National Institute of Environmental Health Sciences (NIEHS), National Toxicology Program (NTP), and National Library of Medicine (NLM).

Applying the 1 L/day estimated intake from drinking water of a 10 kg child used to derive CDC/ATSDR's DW advisory of 1 mg/L (or 1 ppm), this DW advisory value can be expressed in mg/kg-day as follows:

DW advisory (mg/L) × Intake ÷ BW = DW advisory (mg/kg-day)

1 mg/L × 1 L/day ÷ 10 kg = 0.1 mg/kg-day

In the absence of any available pharmacokinetic information on MCHM, route-to-route extrapolation of CDC/ATSDR's DW advisory (derived to be protective of children) to an extrapolated short-term inhalation screening level can then be derived as follows:

Extrapolated Short-term Inhalation Screening Level = DW advisory × (BW ÷ IR)

= 0.1 mg/kg-day × (10 kg ÷ 17.3 m^3/day)

= 0.06 mg/m^3

Where:
- BW = Body weight of a child (10 kg)
- IR = Inhalation rate for a child 1 to < 2 years old (U.S. EPA, 2011; calculated using the recommended mean light intensity short-term exposure value for inhalation of 1.2×10^{-2} m^3/min × 60 min/hr × 24 hr/day).

Extrapolated Short-term Inhalation Screening Level converted to ppm (in air):
Air Conc (ppm) = Air Conc (mg/mg^3) ÷ Molecular Weight of MCHM × 24.45

Air Conc (ppm) = 0.06 mg/m^3 ÷ 128.21 × 24.45

Air Conc (ppm) = 0.01 ppm (in air)

Important Limitations and Uncertainties:

It is important to note that the information presented herein provides an extrapolated short-term inhalation screening level for MCHM that is not intended to provide conclusive estimates of actual risk from inhalation exposures of MCHM, or generate remediation/cleanup goals. Additionally,

cognizance of the several limitations and uncertainties associated with the derivation of this extrapolated short-term inhalation screening level is essential.

First, an oral route-to-inhalation route dosimetric extrapolation does not account for efficiency of respiratory tract deposition and distribution of a chemical, biological and physicochemical factors, and other potential inhalation exposure scenarios (e.g., continuous versus intermittent exposure) that may affect uptake and clearance. Therefore, this simple extrapolation method implicitly assumes that the route of exposure is unrelated to the delivered target organ dose, which is not supported by the fundamental tenets of dosimetry or toxicokinetics. Additionally, if MCHM undergoes a first-pass effect, the blood concentration of the parent compound from oral exposure may be lower than the blood concentration following inhalation exposure at an equivalent concentration.

Second, although CDC/ATSDR used the best available repeated-dose oral toxicity study conducted on MCHM in animals to derive its DW advisory, the test compound used in the study was pure MCHM which is only comprised of the major constituent of crude MCHM (the actual compound that was spilled, composed of a mixture of synthetic chemicals).

Third, although the database lacks inhalation studies on MCHM, a potential for pulmonary portal-of-entry effects may exist as indicated by the observation that MCHM is a dermal and ocular irritant in animal studies (HSDB, 2014).

Finally, due to the short-term-duration of the oral study used to derive CDC/ATSDR's DW advisory and the uncertainty associated with applying this value to longer duration oral exposures, the extrapolated short-term inhalation screening level is not applicable to longer-term/chronic-duration inhalation exposures.

References:

CDC/ATSDR (Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry). (2014). Summary Report of Short term Screening Level Calculation and Analysis of Available Animal Studies for MCHM.

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